27. (4x amended) A method of treating a malignant tumor in a subject wherein the malignant tumor comprises tumor cells around which tenascin has been deposited, which comprises administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein (a) the leukocyte cells are selected from the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells, and (b) the agent is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP (SEQ ID. NO:2), in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin so that the leukocyte cells reach and kill the malignant tumor cells, so as to thereby treat the malignant tumor.

REMARKS

Claims 27-39 and 41 are pending and under examination in the subject application. Applicants note that in a March 15, 2000 Communication in Reply to December 15, 1999 Office Action, applicants elected with traverse Group III of the Restriction Requirement (i.e., claims 27-41). Applicants, hereinabove, have cancelled all non-elected claims (i.e., claims 1-26 and 42-54). Applicants also note that claim 40 was canceled in a November 3, 2000 Amendment in Reply to June 7, 2000 Office Action. Claim 27 has been amended. Support for the amendment to claim 27 can be found in the specification at, *inter alia*, page 13, line 37 through page 14, line 9. Applicants maintain that this amendment raises no issue of new matter. A marked-up version of the amended claim is attached hereto as **Exhibit A** pursuant to the requirements of 37 C.F.R. §1.121. Accordingly,

claims 27-39 and 41 will be pending and under examination upon entry of this Amendment.

In view of the remarks set forth below, applicants maintain that the Examiner's outstanding rejections have been overcome and respectfully request that the Examiner reconsider and withdraw same.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 27-39, and 41 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

In response, applicants respectfully traverse the Examiner's rejection.

Briefly, claims 27-39 and 41 provide a method for treating a malignant tumor, wherein the tumor comprises tumor cells around which tenascin has been deposited. This method comprises the step of administering an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells wherein the leukocyte cells are selected from the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells. The agent can be an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP.

In the Office Action, the Examiner stated that "with regard to claim 27 and dependent claims thereof in the recitation of the term 'effective amount', it is unclear from the specification as to the amount intended."

35 U.S.C. §112, second paragraph, states "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."

Applicants maintain that there is no requirement that a numerical range be recited in the claim or the specification so long as the meets and bounds of the invention can readily be determined by one of ordinary skill in the art. Specifically, claim 27 clearly states the function which is to be achieved by the amount administered. That is, claim 27 recites, in relevant part, that an effective amount of the agent is an "amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and enhance the migration of leukocytes through the tenascin."

Furthermore, applicants note that M.P.E.P. §1504.04(II) states that "the definiteness of the language employed must be analyzed - not in a vacuum, but always in light of the teaching of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 439 F2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971).

Applicants also note that M.P.E.P. §2173.05(c)(III) states that "[t]he common phrase 'an effective amount' may or may not be indefinite. The proper test is whether or not one skilled in the art could determine specific values for the amount based on the disclosure. See *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975)."

Applicants contend that one skilled in the art could determine

specific values for an effective amount based on the specification, at the time of the invention, according to known, routine methods of dose optimization.

In light of the prior art and the specification, it is clear what the term "effective amount" would encompass, as it would be possible for one of skill in the art to determine what that amount would be.

The Examiner also stated that "[a]ny amount added if in enough quantity would become inhibitory." Applicants are not clear as to what the Examiner means by this phrase. Nevertheless, applicants contend that the meets and bounds of claim 27 are clear to one skilled in the art, and that a numerical value for an effective amount is not necessary given that the language of claim 27 clearly states, in non-numerical terms, the requirements for an effective amount (i.e., an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and enhance the migration of leukocytes through the tenascin).

The Examiner also stated that "with regard to claim 27 and dependent claims thereof in the recitation of the term 'antibody', it is unclear as to which b1 antibody is being referred. There are multiple b1 intergrin antibodies available that would fall within the scope of the claims, it is not clear if all are intended."

In response, applicant notes that claim 27 recites, in relevant part, "administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein the agent is an antibody..." Applicants assert that it is clear that the scope of claim 27 includes all

antibodies that bind to a β_1 integrin cell surface receptor of leukocyte cells and that are effective "to inhibit signaling mediated by the β_1 integrin cell surface receptor and enhance the migration of leukocytes through the tenascin."

In view of the above remarks, applicants maintain that claims 27-39 and 41 satisfy the requirements of 35 U.S.C. §112, second paragraph, and respectfully request that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 27-39, and 41 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention. The Examiner states that the specification, while being enabled for a method of treating a malignant tumor which comprises the administration of the P4C10 beta 1 integrin antibody, a beta 1 integrin receptor antibody fragment, or a peptide consisting of GRGDSP, does not reasonably provide enablement for a method of treating a malignant tumor which comprises the administration of any and all antibodies to beta 1 integrin.

In response to the Examiner's rejection, applicants respectfully traverse.

35 U.S.C. §112, first paragraph, states that "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to *enable*

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, ..." (emphasis added). "Enablement ... is determined as of the filing date of the patent application." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81 (Fed. Cir. 1986).

"Enablement is not precluded by the necessity for some experimentation such as *routine screening*. However, experimentation needed to practice the invention must not be undue experimentation. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. The term 'undue experimentation' does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. ... Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (emphasis added, footnotes omitted).

"[I]t is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory. What is relevant depends on the facts ..." *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016 (Fed. Cir. 1991).

As described already, this invention is a method of treating a malignant tumor in a subject. The method comprises administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein (a) the leukocyte cells are selected form the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells, and (b) the agent is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP (SEQ ID. NO:2), in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin.

Applicants maintain that the disclosure enables the claimed method. That is, one skilled in the art, based on the disclosure, could practice the claimed method without undue experimentation.

In support of their position that no undue experimentation is required to practice this invention, applicants direct the Examiner's attention to *In re Wands*. In *Wands*, the court finds enablement with respect to an invention *highly analogous* to the subject invention.

Wands involved an appeal from a decision by the Board of Patent Appeals and Interferences sustaining the Examiner's

rejection for lack of enablement under 35 U.S.C. §112, first paragraph, of the claims in U.S. Serial No. 188,735 (the "'735 application").

The invention claimed in the '735 application involved "methods for the immunoassay of HBsAg [hepatitis B surface antigen] by using high affinity monoclonal IgM antibodies." *Wands* at 1402. These antibodies could be obtained using hybridomas which produce IgM antibodies. The Patent and Trademark Office had conceded "that the methods used to prepare hybridomas and to screen them for high affinity IgM antibodies against HBsAg were either well known in the monoclonal antibody art or adequately disclosed ... in the current application." *Id.* at 1404. A *single* hybridoma cell line (designated "1F8") that secretes IgM antibodies against HBsAg was deposited in connection with the '735 application. The applicants of the '735 application did not deposit or otherwise provide structural details of each and every IgM antibody, or even a large number of IgM antibodies, which could be used in the claimed method. Rather, the applicants described the IgM antibodies as having "a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$." *Id.* at 1402. "The sole issue [was] whether ... it would require undue experimentation to produce high-affinity IgM monoclonal antibodies." *Id.* at 1404.

The *Wands* court held, of course, that producing the IgM monoclonal antibodies required to practice the claimed method did *not* require undue experimentation.

The facts of *Wands* closely parallel those regarding the subject application. That is, the '735 application of *Wands* and the subject application both claim methods. Both methods

employ the use of an antibody. In this application, the agent is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP. Both applications have claims which describe the agents in terms of binding specificity function: in *Wands*, as binding to HBsAg with a defined affinity; in this application, as binding to a β_1 integrin cell surface receptor, in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through tenascin. Both applications rely on the fact that routine screening methods would permit identification of further antibodies for use in the claimed methods.

For these reasons, applicants maintain that the holding of *Wands* firmly supports their position that identifying additional antibodies that bind to a β_1 integrin cell surface receptor of leukocyte cells, inhibit signaling mediated by the β_1 integrin cell surface receptor, and enhance the migration of leukocyte cells through the tenascin, would not require undue experimentation.

In support of this rejection, the Examiner makes certain assertions which applicants maintain are flawed. Applicants address these assertions below.

First, the Examiner alleged that the specification "does not reasonably provide enablement for a method of treating a malignant tumor which comprises the administration of *any and all* antibodies to beta 1 integrin." (emphasis added).

In response, applicants again note that the claimed invention is a method which employs compounds. The invention does not

"encompass" the compounds *per se*. Applicants also note, again, that the compounds employed in the claimed method must possess the function set forth in the claims (i.e. inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin). Applicants note that the Examiner has not cited, and applicants are unaware of, any statute, case or rule which requires applicants to recite *any* - not to mention *all* - antibodies for use in the instant method.

The Examiner's states that "one of skill in the art would be forced into large amounts of experimentation because several factor regarding antibodies to beta 1 integrin have not been taught. The specification has not taught what if any effects the binding of the antibody to other cells expressing beta 1 integrin receptors may have on the host, method of screening for other antibodies, and how to determine if the antibodies are available at the site of interest. Furthermore, the specification has not taught how to avoid premature elimination of the antibody from the host or if immunogeneic responses are elicited from any other antibody."

Applicants assert that one of skill in the art would not be forced into undue experimentation to practice the instant invention commensurate in scope to the claims. Agents which fall within the scope of the claims are defined by functional language in that the agent must (i) bind to a β_1 integrin cell surface receptor of leukocyte cells, and (ii) inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin. The scope of the claims, as written, does not encompass factors such as potential side effects and safety of the agents and the bioavailability of the agents. Indeed, such

factors are appropriate for consideration by a regulatory agency, but not the Patent Office.

In view of the above remarks, applicants maintain that claims 27-39 and 41 satisfy the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner rejected claims 27, 28, 29, and 41 under 35 U.S.C. §102(b) as allegedly anticipated by Bourdon et al. (WO 92/07872).

The Examiner stated that "Bourdon et al. disclose of a method of inhibiting the attachment of cells to tenascin comprising the administration of a peptide comprising the sequence of SEQ ID No:2 and further contemplates the use of the method in a human."

In response to the Examiner's rejection, applicants respectfully traverse.

Applicants assert that the Bourdon et al. reference fails to teach each and every element of the claimed invention. Applicants again note that rejected claims, as amended, are limited to specific types of leukocytes (i.e., polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells). Applicants maintain that these specific cell types are not recited by Bourdon et al. and therefore this reference does not teach each and every element of the claims.

In view of the above remarks, applicants maintain that claims 27, 28, 29 and 41 satisfy the requirements of 35 U.S.C. §102 (b) and respectfully request that the Examiner withdraw this rejection.

Rejection Under 35 U.S.C. §102(e)

The Examiner rejected claims 27, 28, 29, and 41 under 35 U.S.C. §102(e) as allegedly anticipated by Ruoslahti et al. (U.S. Patent No. 5,981,478).

The Examiner stated that "Ruoslahti et al. disclose a method comprising the administration of a peptide sequence that comprises that of SEQ ID No:2 and wherein the administration is to a human. Furthermore, Rouslahti et al disclose that integrins are involved in cancer cell metastasis, and that ligands that are able to bind to the ligand may be applicable for the modulation of integrin activities."

In response to the Examiner's rejection, applicants respectfully traverse.

Applicants assert that the Ruoslahti et al. reference fails to teach each and every element of the claimed invention. Applicants again note that rejected claims, as amended, are limited to specific types of leukocytes (e.g., polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells). Applicants maintain that these specific cell types are not recited by Ruoslahti et al. and therefore this reference does not teach each and every element of the claims.

In view of the above remarks, applicants maintain that claims

27, 28, 29 and 41 satisfy the requirements of 35 U.S.C. §102(e) and respectfully request that the Examiner withdraw this rejection.

Summary

In view of the remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any such fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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EXHIBIT A - MARKED-UP VERSION OF THE CLAIMS

27. (4x amended) A method of treating a malignant tumor in a subject wherein the malignant tumor comprises tumor cells around which tenascin has been deposited, which comprises administering to the subject an agent that binds to a β_1 integrin cell surface receptor of leukocyte cells, wherein (a) the leukocyte cells are selected from the group consisting of polymorphonuclear leukocyte cells, monocytes, macrophages, and lymphocyte cells, and (b) the agent is an antibody, a β_1 integrin cell surface receptor-binding antibody fragment, or a peptide comprising GRGDSP (SEQ ID. NO:2), in an amount effective to inhibit signaling mediated by the β_1 integrin cell surface receptor and to enhance the migration of leukocyte cells through the tenascin so that the leukocyte cells reach and kill the malignant tumor cells, so as to thereby treat the malignant tumor.